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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,411	12/08/2003	Paul A. Cox	045007-0307218	3942

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,411	COX ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-33 and 38-42* is/are pending in the application.

4a) Of the above claim(s) *14-18,25-33 and 38-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-13 and 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,5-33 and 38-42* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks and amendments filed 4 November 2005 have been entered. Claims 2-4, 34-37 and 43 – 75 are canceled; claims 1, 5 – 33 and 38 – 42 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

Election/Restrictions

4. Applicant requested that claims 25 – 33 and 38 – 42, drawn to non-elected species be rejoined if the generic claim from which they depend is deemed allowable. At this time, no generic claim is allowable for the reasons set forth herein.

5. Claims 14 – 18, 25 – 33, and 38 – 42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 31 May 2005.

6. This application contains claims 14 – 18, 25 – 33, and 38 – 42 drawn to an invention nonelected with traverse in the reply filed on 31 May 2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

7. Claims 1, 5 – 13, and 19 – 24 are pending and under examination.

Withdrawn Rejections and Objections

8. The following rejections and objections made in the previous office action are withdrawn:

1) The objections to the claims for being misnumbered is withdrawn in light of the newly-submitted and correctly-numbered claims.

2) The rejection of claims 1, 5 – 13, and 22 – 24 under 35 USC 112, first paragraph is withdrawn in light of applicant's amendment.

3) The rejections under 35 USC 102(b) and 103(a). The amendment of claim 1, now limited to humans, is sufficient to overcome the Kibsy reference. However see the rejections under 35 USC 102 and 103 below, necessitated by amendment.

Maintained Rejections and Objections

Claim Rejections - 35 USC § 112

9. Claims 19 – 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting the presence of a neurotoxin in a sample from a human subject, wherein the presence of BMAA is indicative of the presence of a neurotoxin, does not reasonably provide enablement for the prediction of the likelihood of developing a disorder, or the prediction of the severity of the disorder, or the latency period prior to the onset of the disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained for the reasons set forth on pp. 4 – 5 of the previous office action. Applicant presented no arguments or evidence to traverse the rejection. The amendment to claim to limit the subject matter to humans does not render claims 19 – 21 enabling for prediction of likelihood of developing, latency to, or severity of disease. Thus these claims are still not enabled over their full scope.

Rejections and Objections Necessitated by Amendment

Claim Rejections - 35 USC § 112

10. Claims 19 – 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The specification does not teach the artisan what additional steps are necessary for the method to predict the likelihood or latency to develop disease or the severity of disease, or how to distinguish the method in claims 19 – 21 from the method in claim 1. Thus the artisan would not be able to determine the metes and bounds of claims 19 – 21.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 1, 5 – 13, and 22 – 24 are rejected under 35 U.S.C. 102(a) as being anticipated by Slides from presentation to the Trustees of the Edinburgh Botanical Garden, June 2003 (Reference DR on the IDS submitted 12 April 2004; hereinafter "The slides"). There is no evidence that the slides were authored by the inventive entity of the instant application. Thus absent evidence to the contrary the examiner assumes the slides are "by another". This is in contrast to reference CR, slides presented in Stockholm, which clearly indicates on the first slide that all three inventors are authors.

The slides disclose detection of BMAA from human brain tissue, in asymptomatic patients, those with Lytico-Bodig (a synonym for ALS-PDC, see specification, p. 1, final sentence), and those with Alzheimer's disease. The data presented in the slide entitled "Does BMAA cross the blood/brain barrier?" are identical to those of the first ten patients reported in the "Free BMAA" column of Table 3. While the slide does not disclose the protein-bound BMAA, as all the data are identical, the examiner assumes that the protein-bound BMAA was also measured. Thus the reference teaches each element of claims 1, 5 – 8, 10 – 13, and 22 – 24. Claim 9 also is anticipated by the slides, as all patients are at risk for developing a neurological disorder. This reasoning is explained in detail on p. 9 of the office action mailed 2 December 2004. The patient population in claim 9 is not different from that of claim 1, and thus the slides anticipate claim 9 as well.

13. Claims 1, 7 – 10, 22, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Perry (1990. Annals of Neurology 28:12 – 17).

Perry teaches methods of detecting BMAA and BOAA in cerebrospinal fluid. BOAA is defined by applicant as a BMAA derivative (specification, p. 2, first paragraph). Perry teaches the method is performed on CSF samples taken from human subjects. Subjects diagnosed with a neurological disorder (in this case ALS) and asymptomatic (i.e., controls) were used. See Perry, pp. 13 – 14, "Patients and Control Subjects". Perry teaches how to measure many amino acids (p. 14, Biochemical Methods), and teaches that the method is sufficiently sensitive to detect BMAA at a concentration of 500 nM (0.5 umol per liter CSF; see p. 15). While Perry did not find BMAA in the samples, this is not required by the method recited in claim 1. What is required is that the artisan conclude that the presence of BMAA is indicative of the presence of a neurotoxin, and in fact Perry clearly realized that the presence of BMAA or BOAA would be indicative of the presence of a neurotoxin (see p. 15, first full paragraph and p. 16, final paragraph). By finding no BMAA or BOAA in the CSF samples, Perry concluded that no

neurotoxin was present. Thus the reference fairly anticipates claims 1, 7, 8, 10, and 22 – 23. Claim 9 also is anticipated by Perry, as all patients are at risk for developing a neurological disorder. This reasoning is explained in detail on p. 9 of the office action mailed 2 December 2004. The patient population in claim 9 is not different from that of claim 1, and thus Perry anticipates claim 9 as well.

The examiner notes that the claim would also anticipate non-elected claim 25, drawn to CSF, and claims 17 – 18, drawn to ALS.

Claim Rejections - 35 USC § 103

14. Claims 1, 7 – 12, and 22 – 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perry (1990. Annals of Neurology 28:12 – 17), Kisby (1988. Reference JR on the IDS submitted 12 April 2004) and Cox (March 2002. Reference HR on the IDS submitted 12 April 2004) and Banack (August 2002. Oral Session #89, Ecological Society of America Annual Meeting).

Kisby teaches a method of detecting BMAA in tissue samples from subjects that had received BMAA. Kisby teaches detection of BMAA in serum from monkeys and in brain tissue from rats. Kisby does not teach detecting the presence of BMAA in human subjects. Perry does teach a method of detecting BMAA in the CSF of human subjects but does not teach detection in the brain.

Cox teaches that BMAA is biomagnified in flying foxes which live on Guam. The foxes eat cycad seeds (p. 957, middle of second column), which contain BMAA (p. 956, second column). Cox teaches that the foxes can consume up to 2.5 times their own body weight per day, and teaches that this high consumption, combined with a preference for the cycad seed, would be expected to result in biomagnification of the toxin. Cox also teaches that the Chamorro people, who live on Guam, eat flying foxes on ceremonial occasions and at social gatherings. Cox even depicts how the animals are prepared (boiled in coconut milk; see Figure 1). Cox contemplates that consumption of the foxes would be expected to result in significant ingestion of the toxin. Furthermore Cox teaches that the incidence of ALS-PDC dropped after the population of flying foxes dropped.

Banack repeats the major teachings of Cox, namely that the bioaccumulation of cycad toxins in flying foxes, and the subsequent consumption of the foxes by people, leads to

ingestion of large quantities of the toxin. Banack suggests testing for the biomagnified toxins (see final sentence of abstract).

It would have been obvious to one of ordinary skill in the art to test a human brain sample for the presence of BMAA, and to conclude from that result that a neurotoxin is present, with a reasonable expectation of success. The motivation to do so would be to detect the presence of a neurotoxin, which is indicative of neurological disease. Perry and Kisby both teach how to detect BMAA; Kisby particularly teaches how to perform the method on primate brain tissue and Perry teaches that the method can be performed on human samples, thus it would be reasonable to expect success when performing the method on human brain tissue. Cox and Banack provide the motivation to perform the method on human tissue; in fact Banack specifically recommends testing for the biomagnified toxins.

15. Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perry, Kisby, Cox, and Banack as applied to claim 1 above, and further in view of Duncan et al. (1990, reference LR from the Information Disclosure Statement filed April 12, 2004) and Duncan et al. (1992. J. Neurosci 12:1523 – 1537, cited in office action mailed 2 December 2004),

None of Perry, Kisby, Cox, or Banack teach measuring both free and protein-bound BMAA. As set forth in the previous office action, the two Duncan references teach measurement of both free and protein-bound BMAA. It would have been obvious to one of ordinary skill in the art to detect both free and protein-bound BMAA, with a reasonable expectation of success. A motivation to do so would be to allow detection of all the BMAA in the sample, thereby being better able to correlate the level of BMAA with the presence or risk of acquiring a disease.

Applicant argues, on p. 6 of the remarks filed 4 November 2005, that the combination of Kisby and Duncan alone do not teach or suggest measurement of BMAA in a human sample. The examiner agrees, however the references cited above (Cox and Banack) both provide motivation to perform the assay on human samples. Additionally the reference by Perry specifically teaches performing the assay on human samples.

16. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Perry, Kisby, Cox, and Banack as applied to claim 11 above, and further in view of Schmidt (1998. Acta Neuropathol 95:117-122) and Forman (2002. American Journal of Pathology 160:1725 – 1731, cited by applicant on IDS filed 12 April 2004).

None of Perry, Kisby, Cox, or Banack teach detecting BMAA in patients with Alzheimer's disease. Schmidt teaches that patients with ALS-PDC and those with Alzheimer's disease both have amyloid plaques that are similar. While Schmidt was unable to detect the tau abnormalities that are typical of Alzheimer's disease, Forman teaches both diseases are characterized by insoluble hyperphosphorylated tau and by alpha-synuclein deposits (see p. 1730, first column). Furthermore Forman suggests that there is a common mechanism between ALS-PDC and Alzheimer's (p. 1730, final paragraph).

It would have been obvious to one of ordinary skill in the art to test human samples for the presence of BMAA, wherein the presence of a detectable level of BMAA is associated with Alzheimer's disease. The motivation to do so would be to diagnose Alzheimer's disease, and this motivation comes from both Schmidt and Forman, who teach that similar mechanisms underlie the pathologies of both diseases.

Conclusion

17. No claim is allowed.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
December 13, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
12-21-05